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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,545	ZLOKOVIC ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-22,24,25 and 27-32* is/are pending in the application.

4a) Of the above claim(s) *8-11,21,22,24,25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-20 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/3/05,7/12/05,5/31/06,7/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 14 July 2008 have been entered. Claims 8 – 22, 24 – 25, and 27 – 32 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group 2 (claims 12 – 20 and 29 – 32) in the reply filed on 14 July 2008 is acknowledged. The traversal is on the ground(s) that even though the claimed inventions are patentably distinct (remarks, p. 7, third paragraph) inventions 2 - 13 should be examined together. According to applicant, examination of each of groups 2 - 13 together would not constitute a serious burden. This is not found persuasive because contrary to applicant's assertion, examination of all claimed inventions, or even each of groups 2 – 13, would in fact constitute a serious burden. For example, consideration of elected group 2 requires search for administration of certain products. Claims 24 – 25, which correspond to groups 4 – 5 in the restriction requirement mailed 12 July 2008, require providing a library of candidate agents and determining p53 signaling activity (claim 24) or receptor activity (claim 25). Neither of these steps is required for the methods of group 2. Consideration of groups 4 and 5 would require search for the starting materials and the steps recited in the claims, and such search is neither necessary nor sufficient for determining patentability of the method of group 2. Additionally, certain other claims (21 - 22 and 27 - 28) recite the "use" of certain products, but do not specify the steps to be undertaken in the claimed uses. Thus the searches required for consideration of group 2 would not be informative as to the novelty or non-obviousness of the inventions of groups 3 and 13. Note that the discussion above is exemplary and does not touch on all non-elected groups, but nonetheless provides evidence that consideration of all of groups 2 – 13 together would be burdensome.

As a courtesy to applicant, the requirement for further restriction to a single mutation from among the several recited in claim 20 is vacated. The examiner concedes there is not a serious search burden to find all listed mutations, as they are described in Gale 2002 (Journal of Biological Chemistry 277:28836-28840; see for example p. 28836 second column first complete paragraph. Claim 20 is under examination over its full scope.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 8 – 11, 21 – 22, 24 – 25, and 27 – 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no

allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 14 July 2008.

4. Claims 12 – 20 and 29 – 32 are under examination.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 19 – 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is confusing because it recites the language "A method of providing treating cell stress or injury". It is unclear whether the method of claim 8 is intended to be a method of providing injury or treating injury. Deletion of either of the words "providing" or "treating" would clarify the scope of patent protection sought.

Claim 19 is confusing because it is unclear how the activated protein C is effective in treating diseases including stroke (note claim 19 depends from claim 12, which encompasses treatment of stroke), and is present in an amount that does not provide a therapeutic effect as an anticoagulant, since activated protein C is known to inherently function as an anticoagulant; see for example Gale 2002 (Journal of Biological Chemistry 277:28836-28840), particularly first paragraph.

Claim 20 is confusing because it refers to specific residues of a protein by number (residues 191-193, 229, and 230), but does not recite a reference sequence. Reference to specific residues within an undefined sequence is confusing, and the scope of desired patent protection cannot be determined. Additionally, it is noted that claim 20 does not refer to a single protein, but rather encompasses variants of activated protein C, which the specification defines to include mutated and truncated proteins (see for example p. 14 - 15 and p. 16 lines 24 - 26). Since claim 20 includes variant proteins, it is unclear what residues are referred to by the numbers.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 – 20 and 29 – 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Independent claim 12, as well as all dependent claims, encompass methods of using variants of activated protein C (APC) as well as prodrugs. The examiner concedes that the structure of activated protein C is considered described, as it is well-known in the art; see for example Griffin WO 01/56532, published 9 August 2001. However, the full genus of variants and prodrugs has not been described by the specification. First, it is noted that claim 12 as written is very broad in that it is not limited to administration of prodrugs of activated protein C, but rather lists "…an effective amount of activated protein C, at least one prodrug, or at least one functional variant thereof". That is, the claim is drawn to administration of either any prodrug or variant thereof, or in the alternative to activated protein C. While the specification very generally contemplates administration of prodrugs and variants of APC (see for example p. 6 line 28, p. 12 lines 24 - 26 which refers to certain specific mutants of APC that retain anticoagulant activity, as well as p. 15 first complete paragraph), the specification fails to disclose the structures that are common to all members of the genus of proteins to be administered. Factors to be considered when determining compliance with the written description requirement include, but are not limited to, disclosure of complete or partial structure, chemical formulae, diagrams, or functional recitations when coupled with a known or disclosed structure-function correlation. See for example the Written Description Training Materials, available on USPTO's website at http://www.uspto.gov/web/menu/written.pdf , particularly p. 1 which describes the criteria. In this case, since the specification fails to disclose the structures common to all prodrugs, whether or not they are prodrugs of activated protein C, and all variants of either activated protein C, prodrugs of same, or prodrugs of some other product, the written description requirement has not been satisfied. Note that claim 20 is included in this rejection. While it appears to refer to two variants, since it uses open claim language ("is comprised of at least one mutation...") the claim encompasses administration of variants with an unlimited number of possible structural changes, as do all other claims subject to this rejection.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12 – 14, 16 – 17, 19, and 29 – 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffin (WO 01/56532, published 9 August 2001).

Griffin teaches administration of activated protein C (APC), as recited in independent claim 12, is sufficient to treat several diseases, including ischemic stroke, as encompassed by claim 16, and neurodegenerative diseases including Alzheimer's disease as encompassed by claim 30 and recited in claim 31. See Griffin, p. 14 lines 20 – 30. Griffin teaches that when the patient treated is a human, human APC should be used, as recited in claim 13; see p. 20 lines 18 – 25. The cells that are treated are in the brain, since these are diseases of the brain. Thus the reference anticipates claim 14. Claim 17 is anticipated as Griffin teaches that a dose of 0.01 mg/kg/hour can be given for four hours (see p. 21 line 1 – 14), which equates to 0.04 mg per kg of body weight. Although claim 19 is confusing, it is included in this rejection as well, since the claim does not recite any specific amounts of the APC to be administered, and the reference teaches that APC has therapeutic effects other than anticoagulant effects, including anti-inflammatory effects (see p. 11 lines 9 - 13). As the prior art reference teaches administration of effective amounts of APC for treatment of diseases encompassed by claim 19, it is presumed that the relevant function recited in claim 19 (i.e., not providing certain effects) is provided. Claim 29 is included in this rejection as it recites effects which will happen upon administration. Note no further limitations with respect to dose or timing of the agent administered are recited, nor are any specific drugs named, nor are any additional steps required. Claim 32 is anticipated as Griffin teaches that the APC is to be administered for four to 48 hours (p. 21 lines 1 – 2), which is less than 72 hours.

8. Claims 12, 14, 16 – 19, and 29 – 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Ciaccia (WO 01/72328, published 4 October 2001).

Ciaccia teaches treatment of several diseases by administering activated protein C (APC) to patients with these diseases including Alzheimer's disease as encompassed by claims 12 and 30 and recited in claim 31. See for example Ciaccia, p. 11 line 29 - p. 12 line 9, which lists the particular diseases that APC can be used to treat; see also p. 29 lines 18 – 27. Claim 14 is anticipated as the cells which will be treated are in the subject's brain, since Alzheimer's disease is a disease of the brain. Claim 16 is anticipated as Ciaccia teaches APC is to be administered to patients for treatment of ischemic reperfusion injury; see p. 13 line 30 – p. 14 line 5. Claims 17 – 18 are anticipated as Ciaccia teaches that the APC can be administered at 0.01 mg/kg/day, twice a day, for one day, leading to a total dose of 0.02 mg/kg/day (p. 19 lines 11 – 14). Although claim 19 is confusing, it is included in this rejection as well, since the claim does not recite any specific amounts of the APC to be administered, and the reference teaches that APC has therapeutic effects other than anticoagulant effects, including inhibiting inflammatory cytokines; see p. 14 lines 7 - 11. Claim 29 is included in this rejection as it recites effects which will happen upon administration. Note no further limitations with respect to dose or timing of the agent administered are recited, nor are any specific drugs named, nor are any additional steps required. Claim 32 is anticipated as Ciaccia teaches that the APC is to be administered for one day (p. 19 lines 11-14), which is less than 72 hours.

9. Claims 12 – 13, 16, 19, 29, and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffin (U.S. Patent 5,084,274, issued 28 January 1992).

Griffin teaches treatment of ischemia, recited in instant claim 16 and encompassed by claim 12, by administration of activated protein C. See for example Griffin, claim 1. Claim 13 is anticipated as Griffin teaches that human patients should be treated with human APC; see column 7 lines 15 – 21. Claim 19 is included in this rejection as the claim does not recite any specific amounts of the APC to be administered. Claim 29 is included as it recites effects which will happen upon administration. Claim 32 is anticipated as the reference teaches short-term (30 – 60 minute) administration (column 5 lines 40 - 50), which is less than 72 hours.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 – 17, 19, and 29 – 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin (WO 01/56532, published 9 August 2001) in view of Kureshi 1994 (Neurosurgery 35(5):822-830).

The reasons why Griffin anticipates claims 12 – 14, 16 – 17, 19, and 29 - 32 are set forth in the rejection under 35 USC 102(b) above. Briefly, Griffin teaches administration of activated protein C (APC) for treatment of several forms of cell stress or injury, including ischemia. Griffin teaches that the positive effects of APC are due to its ability to act as an anti-inflammatory agent; see for example p. 9 lines 15 – 16, lines 26 – 27, and p. 11 lines 9 – 13. However, Griffin does not explicitly teach ameliorating the symptoms of brain radiation injury by administering APC to subjects suffering from this condition, as recited in claim 15 and encompassed by claim 16.

Kureshi teaches that brain radiation injury is characterized by inflammation; see for example p. 822 second paragraph, where the reference teaches that patients who receive radiation therapy often experience edema, as well as p. 825 second column, where the reference teaches that these patients typically show high levels of cytokines, which are inflammation-producing molecules. However Kureshi does not teach administration of activated protein C to these patients.

It would have been obvious to one of ordinary skill in the art to use the methods disclosed by Griffin, namely administration of activated protein C for ameliorating inflammatory conditions, to treat patients with brain radiation injury, as suggested by Kureshi, with a reasonable expectation of success. The motivation to do so would be to successfully ameliorate the inflammation that is caused by brain radiation injury. It would be reasonable to

expect success, since Griffin teaches that APC is useful in ameliorating several types of inflammation, including that within the brain caused by stroke, and Kureshi teaches that patients who have undergone brain radiation are in need of such an inflammation-reducing treatment.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12 – 14, 16, 19, 29 - 30, and 32 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 7 of U.S. Patent No. 7,074,402. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass administration of the same product (activated protein C) to the same patient population. Note claims 15, 17 – 18, and 31 are not

subject to this rejection, as the specific limitations recited in those claims are not claimed in the '402 patent.

12. Claims 12 - 13, 16, 17 - 19, 28, and 32 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 36 of U.S. Patent No. 5,084,274. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass administration of activated protein C to patients with ischemia as recited in instant claim 16. Note the ischemia recited in claim 16 is not limited to cerebral ischemia.

13. Claims 12 – 17, 19 – 20, and 29 – 32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 8 – 12, and 60 – 66 of copending Application No. 10/886766. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass administration of the specific mutants recited in instant claim 20 for treatment of the same diseases and conditions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 12 – 17, 19 – 20, and 29 – 32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 12 and 42 - 49 of copending Application No. 11/589371. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims encompass administration of the specific mutants recited in instant claim 20 for treatment of the same diseases and conditions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 12 – 14, 16 - 19, 28, and 32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 16 of copending Application No. 11/632850. Although the conflicting claims are not identical, they are

not patentably distinct from each other because in each case they encompass administration of activated protein C to subjects suffering from stroke

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
September 15, 2008